Professional Literature Overview

Blue Light - Digital Eye Strain (DES) - Vitamin D and Their Effect on Ocular

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Blue Light and Its Effect on the Ocular

1.1 Blue Light Introduction

Abstract

The blue light of the spectrum includes short wavelengths up to 500nm. This high-energy light is primarily derived from the sun, but modern technology, including artificial environment lighting and digital screens, have become a significant source. Over the past few decades, science has been investigating the advantages and detriments that come from exposure to this light.

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Visual Spectrum

Light is essential for life. Science has discovered that light is divided into waves where the length of each wave can be measured in nanometers [1]. A segment of these wavelengths is visible to the human eye, known as the visual spectrum, and perceived as colors when absorbed in the retina's photoreceptors[2]. Apart from color qualities, wavelengths have additional characteristics, energy potential, and influence on their surroundings which actualizes as the light travels from medium to medium [3-6].

Ultraviolet and Blue Light

One segment of light is known as ultraviolet and blue light, which consists of the short-wavelength end of the spectrum. In this spectrum region, individual photons have enough energy to induce photochemical changes in absorbing molecules [7-10]. The primary natural source of this light is the sun, which was the only source until electricity and incandescent lights were introduced [11-13].

Light Emission on Digital Screens

This artificial light has a similar spectrum, though slightly skewed to the red, long-wavelength end [7]. In an attempt to reduce energy consumption, modern light bulbs have evolved to compact fluorescent lamps (CFLs) and light-emitting diodes (LEDs), which have more blue spectral emissions [14-17]. Digital screens also use LED technology due to their high luminous efficiency, durability, and small size [18-21]. LED lights are so pervasive that they are even in technology such as appliances, thus blue light-emitting sources surround people as never before in history. It must be appreciated that the amount of high-energy light emitted by the sun far surpasses that emitted from electronic devices [22-25]. A calculation of fifteen minutes outside has been shown to equate to between ten to thirteen hours of looking at digital devices [18].

The delicate balance between excess penetration of part of the blue spectrum light being a hazard versus blue light as essential for healthy living is one science is still investigating [26-30].

Blue Light Characteristic

Recent research has confirmed the peak of blue light hazard at 435 nm, with an action spectrum from 415 to 455 nm [31, 32]. However, one must keep in mind that the degree of effect is related to various factors, including the intensity of the light, distance of illumination, and the direction of the line of sight [26, 27, 33]. The concentration in irradiance increases up to a hundred times between the cornea and the retina due to the refractive power. This penetration of optical radiation is a biohazard, yet light is an essential component in the visual process. The longer blue light wavelengths, around 470nm, have been demonstrated to be essential for well-being, influencing the circadian rhythm and hormone secretion [26, 27, 32, 33]. The atmospheric ozone layer surrounding the earth provides a protective barrier from harmful ultraviolet rays up to 330 nm by filtering some and attenuating other

wavelengths [34-37]. The thinning of this layer, latitude, time of year, and specific location all affect the quality of this protection [38-40].

Photochemical Damage of the Retina

There are two main mechanisms by which light damage occurs in the retina, the eye's most sensitive and nonregenerative tissue. These mechanisms occur with slightly different absorption and spectral region [41-44]. The first is defined as resulting from relatively low intensity and very long exposure. The damage from this exposure appears to result from absorption within the light-sensitive cells [45-47]. Short wavelength or blue cones seem to be the most sensitive. The second type of damage results from relatively high intensity, short exposures [48-52]. In this case, the primary damage seems to present in the retinal pigment epithelium and is thought to be associated with absorption by lipofuscin [18].

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1.2 Physiological Effect of Blue Light

Abstract

As the human eye is composed of various unique tissues, blue light will also affect each differently. Blue light's impact is influenced by time of exposure, intensity, distance, and direction. Natural tissue absorbing characteristics of structures such as the cornea and intraocular lens prevent severe damage, but what does manage to advance can be either beneficial or harmful. The former can include Vitamin D and melanin synthesis, regulation of the circadian rhythm. In contrast, excessive exposure can be harmful to cells by causing oxidative stress, inflammation, and ultimate death to cells in all ocular structures.

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Blue Light

Blue light is acknowledged as wavelengths up to 500 nm, the 400-500nm portion defined as high energy visible light. As the human eye is composed of various tissues, each with unique characteristics, the permeation of blue light will affect the multiple ocular segments differently [1-4]. The degree of blue light's effect is related to various factors, including the intensity of the light, distance of illumination, and the direction of the line of sight [5]. The corneal tissue naturally absorbs wavelengths below 315 nm and drastically attenuates the 315-400 nm wavelengths [6-8]. Most of what remains is absorbed by the lens, and what manages to progress is further filtered through the vitreous. Ultimately, some radiation reaches the retina and optic nerve[9]. This discussion will focus on this light's long-term effects rather than from acute high-intensity exposure [10, 11].

Blue Light Exposure

Lids surround the eye, and though it is not the center of this discussion, the effects of blue light on this thin skin tissue should be mentioned. Ultraviolet (UV) light is associated with positive health effects as it catalyzes Vitamin D synthesis and triggers melanin production when in contact with epidermis cells, thus in proper quantity reduces the incidence of several autoimmune diseases and cancers .[12-15] Studies have established that excess exposure to ultraviolet (UV) light is a significant cause of skin aging. The blue light of visible light (400-500nm) has also been demonstrated to have harmful effects on skin by causing oxidative stress and destruction of flavin chromophores[5, 16-20]. One study found that visible light-induced increased skin pigmentation was more sustained than that induced by UVA radiation, but the effects are skin type-dependent [21].

Blue Light and Oxidative Damage

The first structures that encounter blue light as it travels towards the eye are the cornea and conjunctiva. Surface exposure to blue light significantly decreases cellular viability by increasing reactive oxygen species (ROS) production in corneal epithelial cells and then triggers inflammation of corneal epithelial cells induced by hyperosmotic pressur[5, 22-28]. The oxidative damage and apoptosis lead to additional ocular inflammation, so the cycle continues[22, 29-32]. It seems blue light's effects on the cornea are not limited to the epithelial cells but also has an inhibitory effect on corneal stromal cell activity, dependent on dose and time[14, 16, 33-39].

Blue Light Phototoxicity Molecular Damage

Blue light exposure can generate pro-inflammatory factors and vascular dysplasia release, which can induce blood vessel permeability [16, 40, 41]. Subsequently, harmful blood components such as immune complexes and lymphotoxin can leak into the retina [42-44]. A break of the blood retinal barrier can ultimately cause photoreceptor cell damage [5, 45]. The retinal damage by blue light has been labeled by researchers Ishii and Rohrer as the "bystander effect" because of the ability to cause local photo-oxidative stress and indirectly induce biological effects in adjacent cells[45].

Blue Light Phototoxicity on the Ocular Surface

Conjunctival epithelial cells have shown even greater photosensitivity than the corneal epithelial cells [5, 33]. Conjunctival pterygium is one manifestation of long-term exposure to ultraviolet sun rays. Hyperosmolar stress (such as a dry environment or an eye overexposed due to decreased blinking and increased dehydration of tears) potentiates blue light phototoxicity, increasing inflammation, altering mitochondrial membrane potential, and triggering the glutathione-based antioxidant system [33, 45], suggesting dry eye patients may be more susceptible to blue light toxicity [46]. Studies have shown that blue light can induce ROS production in the mitochondria of lens epithelial cells, as in the cornea, which may contribute to cataract formation. Alternatively, exposure to blue light can induce dry eye as the blue light triggers the release of inflammatory factors, reduces the secretion of tears and mucin, increases tear film instability, promotes the evaporation of tears [5, 33, 46-48].

Blue Light Phototoxicity in the Crystalline Lens

The intraocular lens contains substances including proteins, enzymes, and protein metabolites which absorb short wave blue light. These substances are continuously added to the lens's protein to produce yellow pigments, causing the lens gradually to darken and turn less transparent.

Blue light absorption by the lens increases significantly, blocking potential retinal damage by these rays [7, 8, 49].

Blue Light Phototoxicity in the Retina

Research has suggested that oxidative stress is considered an important mechanism in the pathogenesis of age-related cataracts[45]. Retinal phototoxicity has been demonstrated primarily as a result of high energy wavelengths of up to 455 nm. Blue light adversely affects the retina using several mechanisms. These mainly include oxidative stress response, upregulating ROS production, which causes mitochondrial and lysosomal dysfunction, and disrupting the epithelial barrier, culminating in inflammatory apoptosis, mitochondrial apoptosis, and DNA damage[5, 45]. Blue light can also affect optic nerve conduction by inhibiting mitochondrial activity[16, 40, 41]. These pathological changes may contribute to various eye diseases, such as diabetic retinopathy or glaucoma [5, 7, 26, 28, 50, 51]. Studies have exhibited accelerated AMD occurrence and development caused by blue light even many years after cataract surgery.[42, 45, 52-60]

Blue Light Benefits

There are positive physiological influences from blue light irradiation. Epidemiological evidence has demonstrated that outdoor activities seem to prevent myopia development [61-64]. The primary difference between digital screen use and outdoor activities is the exposure to natural sunlight, which is more concentrated in short-wave blue light than artificial light sources[61-64]. Though not completely understood, this exposure has been proposed to reduce the eye length via retinal dopamine release. In addition, research has also shown how essential blue light was for reducing astigmatism during development. Animal experiments have exhibited that monochromatic short-wave blue light inhibited the growth of the eye axis and the glass cavity in guinea pigs to produce relative hyperopia.[45]

Blue light has exhibited antibacterial properties in various wavelengths from ultraviolet to 412 nm, 440nm, and 450 nm. Particular attention has been given concerning treating corneal ulcers containing methicillin-resistant Staphylococcus aureus (MRSA) infections[65-68]. Experiments to eradicate infection have been attempted both in combination with riboflavin and in isolation. Some concentrations and protocols have effectively controlled corneal ulcers. Utilizing this data will further develop accurate, effective procedures, and this treatment method is expected to be used in the future.[45]

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1.3 The Visual Effect of Blue Light

Abstract

It has been discovered that blue light is absorbed both by retinal photoreceptors and nonvisual retinal ganglion cells known as ipRGCs. The visual impact goes well beyond perceiving the color blue, influencing dynamic visual acuity and oculomotor function. Blocking blue light from entering the eye has been shown to affect chromatic contrast, glare disability, and photostress recovery time.

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Introduction

Blue light includes the short-wave end of the spectrum and is refracted more as it travels through mediums than the longer wavelengths. The exact nanometer of this segment of the color spectrum is not clear cut but generally accepted to include up to 500nm, where 400-500nm is considered high energy visible light[1-3]. The central fovea is known to be tritanopic, or blind to this blue–light[4]. This same area is one with the highest potential for acuity. These physical traits affect visual clarity and perception when full spectrum light reaches the retina[5].

Retina and Blue Light

Blue light's short wavelength and high refractive angle mean it will focus not in the center of the retina but instead in the front of the retina. Long exposure time to blue light has been shown to cause symptoms of visual fatigue such as diplopia, blur, or inability to concentrate, which affects learning and working efficiency. [6-8]
Blue light and Visual Functions
Blue light contributes to visual functions well beyond static color perception and acuity, though often only under specific conditions. As information from research emerges, these characteristics can help decide when to enhance and when to block blue light from entering the eye more precisely [9, 10].

Circadian Rhythm and Blue Light

Blue light had been noted in the literature as a parasympathetic activator, and sensory depressant, particularly the region of 465-495 nm, has been established to initiate aspects of the circadian rhythm[9, 10]. Intrinsically photosensitive retinal ganglion cells (ipRGCs), nonvisual photoreceptors, seem to react to this light, as they express melanopsin[11, 12], a blue light-sensitive photopigment [13, 14]. These cells have been discovered to influence the circadian rhythm and have been suggested to enhance alertness. [13-15] IpRGCs are also sensitive to motion perception.

Dynamic Visual Acuity and Blue Light

Dynamic visual acuity pertains to detecting and recognizing a target while either the target or the subject is in motion[16-20]. In one investigation, blue light has been shown to enhance dynamic visual discrimination under difficult task conditions[14], perhaps through this same mechanism. Other research found reduced speed perception between 6-20% when viewing chromatic and achromatic test stimuli through blue-blocking filters[21]. They reported that the lenses that attenuated the most blue-light also produced the most significant decrease in perceived speed, but this was also affected by overall luminance and stimulus color (red and green stimuli were largely unaffected)[21].

Oculomotor Functions and Blue Light

Various researches investigated the influence of blue light on oculomotor functions and found enhanced pursuits compared to orange light. Similarly, saccade speed was enhanced, precisely horizontal shorter saccade latencies with blue light versus orange light[22, 23]. The hypothesis is that the brain regions that are highly correlated with dynamic visual acuity and attention are also correlated with eye movements, such as frontal eye fields (FEF) and cerebellum, which are known to be influenced via the blue-light sensitive ipRCGs[22].

The Benefits of Blocking Blue Light

Blocking blue light from entering the eye has been indicated to prevent multiple adverse physiological aftereffects. Some unintended side effects, particularly at low light or mesopic levels, include reduced color sensitivity, reduced contrast sensitivity, and increased photostress recovery time[24, 25]. Additional factors besides blue light influence abilities such as age, adaptive state, and macular pigments at the time of observation. Other studies have found violet light-filtering intraocular lens (IOL) implants yielded a reduction of cyanopsia and a potential improvement in contrast sensitivity in photopic conditions and background dependent (for example, if the background is blue)[26-28]. The different chromophores of the IOL and various material and design options may also have contributed.[29]Alternative observations reported that blue light-filtering IOLs have demonstrated that they improve chromatic contrast, decrease glare disability but actually decrease photostress recovery time compared to non-blue-filter IOLs. However, an advantage compared to ultraviolet filtering IOLs is inconclusive.[22, 30, 31]

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About Digital Eye Strain (DES)

2.1 Dry Eye Disease Symptoms

Abstract
Dry eye disease (DED) is one of the most prevalent ocular surface disorders, defined as a multifactorial loss of homeostasis of the tear film accompanied by ocular symptoms. This encompasses a cycle of tear film instability, hyperosmolarity, inflammation, and ocular surface damage. Symptoms can be either visual or sensory and do not always correlate with one another.

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Dry Eye Disease (DED) Symptoms
Dry eye disease (DED) is one of the most prevalent ocular surface disorders. After comprehensively reviewing the available international data, DED has been defined as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles"[1]. Though clinically there is generally some overlap, DED has been classified into two subtypes known as aqueous tear-deficient dry eye, distinguished by inefficiency or inability of the lacrimal glands to produce tears, and evaporative dry eye generally attributed to excessive evaporation of the tears[2-4]. The former is typically associated with a compromise in the lacrimal functional unit and often may have an autoimmune element[5-10]. The latter, the more common, involves meibomian gland dysfunction (MGD), which results in modification or reduction of tear fluid lipids, causing compromise to the integrity and quality of the tear fluid[11-15]. MGD can be triggered by numerous pathological mechanisms, including inflammation, microbial contamination, and lipid deficiencies[16]. The plethora of triggers that induce DED includes allergy, surgery, environmental, chemical, or systemic, and each can be the genesis of a vicious cycle that is challenging to break[11-15].
Symptoms of DED are as varied as the causes and range from almost undetectable to visually debilitating, painful, and severely compromising the quality of life[17-21]. Depending on the cause, symptoms can present in the morning, night, or unrelated to a specific time. Patients sometimes present with symptoms they do not associate with DED as the origin[11, 22, 23].
Symptoms can be categorized as visual and sensational. The former would include fluctuating or constant blurry vision, glare, decreased contrast sensitivity, and sometimes these present as the initial complaint[19-21]. Visual symptoms result from an unstable tear film, as a smooth refractive surface is critical for optimal visual performance[1]. Eye fatigue and strain often develop as the patient attempts to continue the task at hand through the blur[11, 19-21, 23].
Watery eyes, frequently a reaction of the lacrimal gland to the lack of a quality tear film, are often experienced as a perplexing symptom from the patients' perspective[24-27]. Furthermore, when the tear film's aqueous layer is decreased, the lipids and mucus layers may contact, resulting in a stringy discharge[11, 19-23].
Patients may complain of itchy, stinging, gritty, or a foreign sensation that stems from a dysfunctional tear film, whose task is to prevent friction between the rough lid and ocular surface[11, 18-20, 22].
Red eye is a general term that can be divided into palpebral conjunctival redness, where a limited horizontal area is red, which derives from the area being exposed too long to the environment, or general conjunctival redness where the blood vessels of the whole ocular surface are engorged to provide nutrients to the area inadequately supplied by the decreased tear film[13, 17, 19-22]. The lid margin can present as red to varying degrees, depending here too on the etiology. Inflammation that causes redness can be produced by MGD, or by exotoxins and bacteria that have not been washed away, or full-blown blepharitis resulting from dry eye, or, in chronic cases, capillary growth into the lid[7, 8, 13, 14, 20].

Symptoms without signs describe a unique scenario when a patient will complain of ocular pain disproportionately greater than the clinical signs. This can be caused by neuropathic pain due either to a lesion or disease in the somatosensory system, and treatment will be targeting pain management differently to DED[16, 28-33]. Similarly, reported symptoms can present in the absence of clinical signs when there is episodic dry eye or a pre-clinical dry eye state[8, 24, 26, 27, 32, 34, 35].
Alternatively, signs of ocular surface disease can be clinically observed, but the patient reports no discomfort. This scenario still may require DED management, as corneal nerve damage secondary to longstanding DED is a recognized occurrence, and the reduced corneal sensitivity can mask discomfort[9, 36-39].
If symptoms are severe, they compromise the physical functioning, social interaction, and general well-being of patients, resulting in a significant deterioration in the quality of life[20, 22, 40].

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2.2 Digital Eye Syndrome and Dry Eye

Abstract

Digital eye syndrome affects almost all users of screens for over three to five hours per day. The dry eye component includes both ocular and visual disturbances due to ergonomic and environmental influences, as well as detrimental behavioral adaptations such as enlarged palpebral fissure and reduced quantity and quality blinking. Treatment would include addressing the surrounding climate and ergonomics, and directly focusing on tear film rehabilitation via re-training proper blink and artificial tears.

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Digital eye syndrome (DES) - Prevalence

Digital eye syndrome (DES) is so common as to be estimated to affect to some degree 90% of individuals who use digital screens for more than three to five hours per day[1, 2]. This currently includes approximately 60 million people around the globe and is ever-growing as screen use only continues to increase [1-6]. For decades a strong association between hours of use and DES has been demonstrated[3, 4].

Definition of DES

The American optometric association initially defined DES as a combination of ocular and visual disturbances an individual feels while working on a computer screen[2, 5-7]. However, over time the definition has evolved and encompasses not only computer screens, but all digital screens [2, 5-11], and the symptoms can persist well beyond the actual usage time[2, 5-7].

DES Symptoms

DES includes a wide range of visual, ocular, and musculoskeletal symptoms, some quite unspecific such as asthenopia, tired or strained eyes, blurry vision, fatigue, headaches, double vision, and dry eye[2, 5-7, 12] .
These general symptoms can be subdivided into visual symptoms, digital screen symptoms, and ocular surface signs[13-17]. The solutions for visual symptoms are primarily optical to correct refractive errors or binocular imbalances, including vergence and accommodative issues[10, 14, 16].
The latter two categories will be further explained in an attempt to understand the etiology and alternative therapy courses[5, 7, 8, 10, 16, 17].
Disability glare is a commonly reported digital screen symptom. Usually, it results from ergonomic factors such as angle of the screen and head angle or screen settings such as a glossy refracting finish, brightness, resolution, or refresh settings[5, 7, 8, 10, 16, 17]. An additional cause for glare can be attributed to an unstable tear film, such as is seen in individuals with dry eyes, which scatters the refracted light [2, 16-19].

Ocular Surface Signs of DES

Ocular surface signs (OSS) typically consist of corneal epithelial and conjunctival fluorescein staining, typically in a "smiley" formation on the inferior palpebral fissure or in the central horizontal area[20]. Contact lens wearers are particularly vulnerable to what is known as lid wiper epitheliopathy, and lid parallel conjunctival folds [2, 16-19].
Several factors cause these OSS. It has been well documented that the blink rate decreases during digital screen use, regardless of the type of screen (computer, tablet, cellphone), which results in elevated dehydration of the tears[2, 14, 16-18]. A correlation was noted between smaller font sizes and a decrease in blinks per minute. This, combined with a larger palpebral fissure, as when looking straight ahead at a computer screen, can cause tear film instability and reduced secretion from meibomian glands[2, 14, 16-18]. This results in accelerated dehydration, dry

eye symptoms, and OSS. An incomplete blink has been detected in individuals looking at the computer screen at primary gaze level and in individuals who habitually look down at tablet or cellphone screens for hours a day[2, 14, 16-18]. Sequelae of this habit are an unstable tear film, Meibomian gland dysfunction, and ultimately dry eye ensues. Additional considerations such as a dry or air-conditioned environment further aggravate the exposed ocular surface[2, 7, 9, 14, 16, 17, 21]. The tear prism which accumulates at the lower lid margin evaporates much faster under these conditions[2, 14, 16-18].

Treatment for Computer Vision Syndrome

Ergonomic attention can help alleviate some of these factors. For example, lowering the computer screen will generally induce an inferior gaze and a narrower palpebral fissure[14, 16]. Induced distance viewing and intentional blinking can be prompted using a timed screen pop-up to break up extended uninterrupted screen time[2, 7, 9, 14, 16, 17, 21].

The most prevalent treatment for dry eye to alleviate symptoms is artificial tears[7, 13, 16]. Development of artificial tears has evolved dramatically from their initial formulas, primarily incorporating hydrogel polymers as the active ingredient. These polymers target the water and, indirectly, the mucin components of the tear film[7, 13, 16]. The hydrogel humectants swell into a gel form, mimicking mucin and forming a viscous membrane which relieves inflammation or irritation, thereby preserving the ocular surface microenvironment, each with unique chemical composition and characteristics[5, 9, 14, 16]. While artificial tears do not increase blink frequency, components can help increase tear endurance and stability, bridging the gap between blinks[5, 9, 14, 16]. Excessive evaporation of tears due to a compromised or absent lipid layer is a hallmark characteristic of evaporative DED[5, 9, 14, 16]. The tear stability is particularly vulnerable, as mentioned, in a decreased blinking environment, such as when observing digital screens. Artificial tear formulations at the forefront integrate active ingredients targeting the lipid layer of the tear film to prevent dehydration[22-24]. The first generation of lipid drop preparations used microemulsions[22-24]. These drops were very viscous and affected visual clarity, though they proved effective at providing a consistent barrier to excessive tear evaporation and superior prophylactic efficacy[25]. Advanced technology incorporates nano-emulsions. These are smaller droplets generally between 20-200nm with a lipophilic phase, a hydrophilic phase, and enough of some surfactant composition to reduce the interphase surface tension but not too much that would cause ocular irritation[26-29]. These nano-emulsions reduce the attractive force between the drops and seem to be affected little by temperature and pH[26-29]. After one month of use, this system has shown a capability to increase the lipid layer of the tear film, improving its stability and reducing evaporation of the underlying aqueous layer[29].

Current formulations generally do not interfere with vision and are usually compatible with contact lenses [30, 31].

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Ocular & Vitamin D

3.1 The relationship between blue light and vitamin D

Abstract

Vitamin D can be sourced in humans either by external ingestion or via biological synthesis, primarily by ultraviolet radiation. Solar radiation is the primary source of blue light. A mutually beneficial harmony is created when ultraviolet light initiates the synthesis of vitamin D. The positive attributes of each component can be actualized, while the adverse effects of the light are diminished by vitamin D.

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Vitamin D

Vitamin D is classified as a hormone because it can be synthesized in the skin and circulates to act at a target different from its source and a vitamin as most populations do not synthesize enough by this biochemical pathway[1].

Sources of Vitamin D

Vitamin D can be sourced in humans either by external ingestion (food or synthetic supplement) or through biological synthesis. The simplified mechanism by which vitamin D, or more accurately D3 (the second form of vitamin D, D2, is only ingested from external sources), is synthesized is as follows: ultraviolet-B radiation (UVB, 280-315nm wavelength) strikes the skin (or any tissue containing vitamin D receptors (VDR)), where a preform of vitamin D3 called cholecalciferol is synthesized from a precursor molecule of the steroid cholesterol called 7-dehydrocholesterol in the epidermis[2]. This vitamin D3 is biologically inert and requires hydroxylation, first in the liver and then in the kidney, to form the biologically active form of vitamin D,1,25(O.H.)2D[2].

Solar radiation is the primary source of blue light. Its' spectral shape and intensity vary with elevation, latitude, season, weather, and even the time of day[3, 4]. Exposure to the short wavelengths of light elicits both visual and nonvisual responses, can both promote aging and control circadian rhythms. One of the positive nonvisual responses of exposure to the sun is the synthesis of vitamin D3. However, that can further vary depending on age and skin pigmentation[2]. This synthesis predominantly occurs in the upper epidermis layers, where the highest concentration of 7-dehydrocholesterol is located. Irrespective of skin type, 70-80% of the skin melanin, the protective cells against photo-damage, is located at the basal epidermis and therefore does not impede with vitamin D production taking place at the upper layers[5]. Low serum concentrations have been observed in high pigmented individuals, and the decrease in skin pigmentation is held to be a necessary evolutional adaptation as people migrated from the equator, but the lower bioavailability is believed to be correlated to the number of pigment genes or genetic variations and not only the actual skin pigmentation[1, 2, 5].

The currently accepted human vitamin D requirement is serum 25(O.H.)D [concentration 30–60 nmol/l], but as evidence emerges, the recommendations for vitamin D status are being reviewed and increased. Vitamin D is necessary for calcium metabolism, a healthy skeleton and plays a role in vascular health[2]. More recently, research has suggested that vitamin D can provide additional benefits, including a protective effect against some cancers (e.g., of colon, breast, prostate), a lowering of blood pressure, and possibly play a role in preventing the onset of some autoimmune diseases such as multiple sclerosis and type 1 diabetes[4]. Excessive radiation from short wavelengths from the sun can be detrimental, cause photoaging, and increase the risk of skin cancer[4]. As the vast majority of vitamin D acquisition comes from sun exposure (90%), not diet or vitamin supplements, this has implications for seeking methods on increasing production safely[4].

Cell homeostasis and health

Autophagy is a catabolic process by which a cell self-eats, degrading its' cytoplasmic contents, engulfed in autophagosomes, and turning them over to the lysosome for elimination or recycling[3, 6]. The process plays a crucial role in cellular homeostasis as autophagy mediates the degradation of cell components, recycled to generate the nutrients [3, 6, 7], and autophagy is upregulated in conditions such as oxidative stress when cells need to remove unnecessary or dysfunctional components[3, 4, 6, 7]. Research has only begun to examine the role of autophagy in the visual system while understanding that virtually all cell types from the cornea in the front of the eye [6]to the retinal pigment epithelium at the back of the eye, rely on one or more aspects of autophagy to maintain structure and normal physiological function[7]. Aging is a significant risk factor for various ocular disorders, including age-related macular degeneration in the retina, cataracts in the lens, glaucoma in the optic nerve, dry eye syndrome in the cornea, and corneal dystrophy[8]. A series of changes occur with aging. Proposed hypotheses to explain the process include increased oxidative stress (the most popular hypothesis currently), decreased mitochondrial energy metabolism, and accumulated mutations[8].

Alterations in autophagy are seemingly involved in several ocular diseases, such as dry eye, pterygium, and retinal neurodegeneration[9]. However, the exact modifications to the autophagy regulatory mechanisms are unclear[9]. One study showed that blue light stimulation could induce impaired autophagy by increasing nucleotide-binding oligomerization domain 2 (NOD2) activation on the ocular surface[9]. Blue light has high photochemical energy and induces cell apoptosis through reactive oxygen species (ROS) overproduction in the ocular surface and the retina, specifically to photoreceptors and retinal pigment epithelial (RPE)[9, 10]. It has been demonstrated that excessive ROS can cause severe oxidative stress and deficient autophagy[9]. Ergo, blue light has been shown to impair autophagy[11]. Increased oxidative stress and inflammatory molecules further aggravate clinical dry eye parameters, such as tear volume, tear film break-up time, and corneal epithelial staining scores[9].

As mentioned, vitamin D can be obtained from nutrient sources or naturally synthesized in the skin. It has been found to influence the survival and fitness of cells through the modulation of autophagy[12]. More recently, autophagy has been implicated in playing an immunomodulatory role to counter environmental stressors in chronic inflammation and models of infection[12]. A recent study showed that vitamin D suppressed skin inflammation and accelerated tissue recovery by upregulating autophagy[12], identifying vitamin D-induced autophagy as a potential therapeutic option for treating ultra-violet-induced acute skin inflammation[12].

Summary

Thus a mutually beneficial balance is created when UVB light and vitamin D meet. U.V. exposure can detrimentally increase oxidative stress, apoptosis, and among its' other recognized attributes, positively trigger the synthesis of vitamin D. Vitamin D synthesis triggered by U.V. light is essential, and it further reduces the detrimental effects caused by the U.V. exposure, allowing for the advantages of both to be realized[13-15].

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3.2 The influence of vitamin D on ocular health

Abstract

Vitamin D is recognized to have many diverse functions, including immune regulation, proliferation, differentiation, apoptosis, and angiogenesis. There is evidence that vitamin D assists in maintaining ocular health, and vitamin D receptors can be found in the cornea, ciliary body, lens, and retina. The multiple loci suggest that vitamin D levels may have a role in developing or preventing ocular diseases such as dry eye, myopia, uveitis, glaucoma, diabetic retinopathy, and age-related macular degeneration.

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Introduction

Vitamin D is recognized to have many diverse functions, including immune regulation, proliferation, differentiation, apoptosis, and angiogenesis. The widespread expression and gene influence suggests vitamin D has pleiotropic effects[1]. There is evidence that Vitamin D assists in maintaining ocular health, and vitamin D receptors (VDR) can be found in the cornea, ciliary body, lens, retina, and retinal pigment epithelium[2]. The multiple loci of VDR suggest that vitamin D levels may have a role in developing or preventing ocular diseases[3, 4]. Appreciable concentrations of vitamin D metabolites can be observed in the tear, aqueous, and vitreous humor fluids[5], and one study measured a significantly higher 25-hydroxyvitamin D level in the tear film than the serum of 48 healthy individuals[6].

For example, epithelial cells in the cornea and conjunctiva can synthesize vitamin D3 metabolites in the presence of 7-dehydrocholesterol (the provitamin cholesterol) following exposure to UVB[5, 6]. Cathelicidins and defensins are primarily found in epithelial cells after activation either by an external infiltration or by 1,25-D (the hormonally active form of vitamin D). They may act synergistically to protect the eye from infections and assist with the conjunctiva and cornea wound healing. Cathelicidin additionally may promote wound healing[7].

One corneal manifestation of a vitamin D deficiency was discussed in a large retrospective study of over 10,000 patients, recognizing and monitoring changes primarily in the cornea and how they correlated to adequate versus inadequate vitamin D status[2]. This clinic utilized the Oculus Pentacam Scheimpflug imaging system (Oculus Optikgeräte GmbH, Wetzlar, Germany) to monitor changes. One consistent corneal vitamin D deficiency distortion pattern described was the development of corneal irregular or against the rule astigmatism involving the central optic zone[2]. This irregular cylinder component is not always observed during manifest refraction, as the mix of flat and steep regions sometimes along the same meridian cancel each other out to some degree while still generating a net loss of resolution. Lower light and contrast conditions, illuminated targets, pixels on digital screens are more prone to negative impact from this distortion. These distortions improved significantly with supplementation or adequate sun exposure, apparent topographically and optically[2].

Dry eye

Research delineating the relationship between dry eye and vitamin D deficiency has been explored since the 1960s, and over the past few years, has been quite extensive. Vitamin D deficiency has been demonstrated to cause symptoms associated with dry eye disease, but the relationship is complex as they are not codependent[8, 9]. Dry eye disease can occur with normal serum vitamin D levels, and other studies found similar vitamin D levels in both dry and non-dry eye patients[10]. The influence of age and the variability in dry eye parameters tested

between studies further obscures a definite direct correlation[10-13]. A meta-analysis of the published literature in 2020 presented that there seems to be a significant association between vitamin D and dry eye disease, specifically a negative correlation with Ocular Surface Disease Index (OSDI) scores[9, 13-18].
Vitamin D induces cytokine IL10 production and reduces additional inflammatory cytokines like IL1, IL6, TNF alpha, and C-reactive protein[8, 9, 19-22]. It further decreases inflammation by increasing antioxidant cytokines in tears and suppressing Th1 and Th2 cells[8, 19]. As vitamin D reduces tear osmolarity, tear film stability will improve and directly affect lacrimal gland function[23].
Vitamin D has an important role in estrogen biosynthesis and signaling. Insufficiency may contribute to dry eye in postmenopausal women, known to have increased dry eye disease and low estrogen levels, which has been implicated as a cause[23].
Past research has suggested vitamin D deficiency is associated with neuralgia and chronic pain. It seems vitamin D can influence the severity of symptoms by modulating nociception, as it affects nerve homeostasis and inflammatory responses.[9] Though the exact mechanism linking vitamin D to pain is still elusive, several hypotheses have been proposed. Firstly, vitamin D deficiency can directly or indirectly influence nociception on nerve fibers: Vitamin D is known to affect serotonin synthesis (serotonin perpetuates pain), which was found elevated in DED patients[9, 24]. Research has also indicated that vitamin D decreases nitric oxide production (a nociceptive neurotransmitter), thereby influencing pain modulation[9]. Vitamin D can inhibit maturation and induce tolerance in dendritic cells[9]. This would interrupt the inflammatory process. Therefore, a deficiency may indirectly induce an inflammatory process.
Vitamin D supplementation decreases ocular surface inflammation and improves several tear film features such as tear film break up time (TBUT), ocular surface staining, eyelid margin hyperemia, and tear secretion[1, 13, 19, 25]. As VDR have been found in ocular barrier cells, it has been suggested that vitamin D also improves corneal epithelial cell barrier function by helping gap and tight junction regulation[1, 23, 26].

Synergistic vitamin D therapy for dry eye
Cyclosporine-A (CsA) 0.05% is a topical immunomodulatory compound with anti-inflammatory properties demonstrated to be beneficial in treating dry eye. CsA affects subconjunctival and lacrimal gland inflammation, after which follows an increase in tear production and conjunctival goblet cell density[26]. It can take a few months for clinical improvement, and a study showed increased improvement when combined with vitamin D supplementation (systemic or buccal spray form)[26]. This study found similar efficacy with either vitamin D supplement modality. They further concluded that combined therapy with CsA was not significantly superior to vitamin D monotherapy[26].
Similarly, topical steroids have long been known to improve dry-eye associated symptoms, signs, and inflammation, enhanced with synergistic adequate availability of vitamin D[2]. Particularly interesting is to consider the enhanced treatment of dry eye signs and symptoms with this combination and add the ability of vitamin D to suppress the steroid effect on intra ocular pressure[2]. The enhanced effectivity of combined steroids and vitamin D has been established to treat psoriasis, another chronic, surface inflammatory condition. It could be explored as a combination topical treatment for the ocular surface[2, 27-29].

Vitamin D and myopia
Myopia development is multifactorial, influenced by both genetic and environmental components. Studies have shown that spending time outdoors is protective against increased axial elongation, evoking investigations in genetic variations and the possible role of vitamin D[1, 30-39]. Polymorphisms in the receptor and its start codon have been linked to myopia progression[2]. Studies have investigated possible VDR variations as myopia risk factors, as the VDR gene is close to MYP-3, loci associated with myopia[1, 30-33]. Vitamin D's ability to regulate calcium levels suggests a possible influence on deterring myopia progression by maintaining calcium homeostasis and consequently ciliary muscle function[1]. In summary, there seems to be a relationship between vitamin D and myopia progression, yet the exact pathway is undetermined[1, 30-36, 40, 41].

Uveitis

Uveitis is an inflammatory condition caused by an infection, or, more commonly, it has an autoimmune etiology[1]. Vitamin D's anti-inflammatory properties influence T cell response and can assist in suppressing autoimmune flares[42-44].

A retrospective study found an increased risk for uveitis, a noninfectious ocular inflammation, in patients with vitamin D deficiency[45] and supplementation, or sun exposure was associated with decreased uveitis activity[46, 47].

Behçet's disease is similarly an inflammatory situation, where more than half the patients with this disease have uveitis. A Chinese study found certain polymorphisms in 7-dehydrocholesterol reductase (DHCR7, necessary for vitamin D production) exhibited susceptibility to Behcet's uveitis, strengthening the possibility of a genetic link between uveitis and vitamin D[1, 45].

Glaucoma

Treatment with vitamin D modulated the expression of several genes involved in intraocular pressure (IOP) regulation in mice and rat cells[1]. Multiple studies have been conducted to determine if and how vitamin D administration will effectively lower IOP, but it is still not an accepted treatment method[48-51]. Whether the status of vitamin D is indicative of a risk factor for glaucoma is also, as yet, inconclusive[1, 52].

Vitamin D3 has been shown to modulate the immune response and decrease angiogenesis in the eye and other organs. Its' neuroprotective effect may be a protective factor for glaucoma, and vitamin D3 deficiency could explain glaucoma occurrence or severity in some patients[48, 53]. The potential physiological role of vitamin D as an anti-inflammatory agent in the oxidative stress-driven pathogenesis of primary open-angle glaucoma has also been considered[53].

The results of a small study group indicated that serum vitamin D levels were lower in patients with pseudoexfoliation syndrome with and without glaucoma, they did not find these levels to be statistically significant, nor have an effect on the development of PEX glaucoma/syndrome or the control of the disorder[12, 26].

In summary, studies suggest vitamin D could affect IOP by modifying gene expression of aqueous humor production or outflow or through neuroprotective effect[52-54]. Vitamin D has been linked to inflammation modulation, which influences neurodegeneration and its severity. Therefore, vitamin D has been suggested to influence inflammation and degeneration of neuronal tissue[48].

Diabetic retinopathy

Vitamin D inhibits neovascularization. This inspired researchers to investigate a possible relationship in diabetic retinopathy. Several studies found an inverse correlation between serum vitamin D levels and the severity of retinopathy[1, 52, 55-65]. Those with proliferative retinopathy had the lowest serum levels of 25(OH) D, some going so far as to consider it a biomarker for development[1, 66, 67].

Age-related macular degeneration (AMD)

Numerous studies suggest that a relative vitamin D deficiency status could be a potential risk factor for the development of early or late AMD[68-82].

Genetic determinants of vitamin D bioactivity have been identified in the vitamin D receptor (VDR) and the retinoic acid-X-receptor (RXRA)[68-72, 83]. RXRA forms a complex with 1,25(OH2)D bound to VDR and is recognized by vitamin D response elements found on genes[73, 74]. McKat et al. found no causal association was determined between the vitamin D genetic pathway and any stage of AMD but did find an association between neovascular AMD and vitamin D deficiency (categorized as <30nmol/l)[70].

Synthesis and bioavailability

Synthesis and bioavailability of vitamin D are affected by age, males versus females, and obesity[19]. When exposure to the sun and UVB is either unavailable or inadequate, vitamin D supplementation currently can be delivered orally or by intramuscular injection. Both are reported to be an effective way to increase and maintain serum 25(OH) D levels[5, 23, 26, 84-88]. Oral vitamin D supplementation affects vitamin D metabolite concentrations in the anterior segment of the eye[5].

One must consider that while a previous 25 (OH) D serum level of 50 nmol/l was considered sufficient for

health, the scientific and health community is reconsidering whether this is the case[89-93]. A global discussion readjusting and increasing recommended levels is underway, keeping in mind that excessive ingestion has its' own potential adverse effect such as hypercalcemia, hypercalciuria, and hyperphosphatemia, followed by their sequelae[94]. This intoxication can occur despite no measurable increase in serum levels of 25 (OH) D, as serum level does not always reflect uptake[94]. To date, there are limited topical options for vitamin D supplementation[67], though the potential benefits of such a product are abundantly clear.

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